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Effect of Brexpiprazole on Prolactin and Sexual Functioning

An Analysis of Short- and Long-Term Study Data in Major Depressive Disorder

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Abstract:

Purpose/Background: Evidence supports use of adjunctive atypical antipsychotics in major depressive disorder (MDD). Impaired sexual functioning is common in MDD and may be worsened by antipsychotic adverse effects. We evaluated the effect of brexpiprazole on prolactin and sexual functioning in patients with MDD.

Methods/Procedures: In short-term studies, patients received adjunctive brexpiprazole 1, 2, or 3 mg or placebo. The long-term study was a flexible-dose (0.5–3 mg/d) open-label extension (OLE). Change from baseline and shifts in prolactin status and prolactin-related treatment-emergent adverse events (TEAEs) were assessed. Sexual functioning was assessed by the Massachusetts General Hospital Sexual Functioning Questionnaire.

Findings/Results: Median changes in prolactin levels from baseline to week 6 in short-term studies were as follows: brexpiprazole, 5.99 ng/mL (females) and 1.61 ng/mL (males); placebo, -0.15 ng/mL (females) and -0.08 ng/mL (males).

Median changes from baseline to week 52 in the OLE were as follows: 0.27 ng/mL (females) and 0.27 ng/mL (males). Prolactin levels in patients with baseline prolactin greater than 1 × upper limit of normal values tended to decrease over time.

The proportion of brexpiprazole-treated patients with greater than 3 × upper limit of normal postbaseline prolactin values in short-term studies for both sexes was low (0%–0.3%) and did not differ from placebo: OLE, 0.5% (females) and 0.8% (males).

In short-term studies, the incidence of prolactin-related TEAEs was 3.1% for brexpiprazole and 0.7% for placebo (OLE, 3.1%). There were overall numerical improvements from baseline in sexual functioning for females and males after short- and long-term brexpiprazole treatment, with statistically significant improvements for brexpiprazole versus placebo in females on the items ‘interest in sex’ (-0.19; 95% confidence interval [CI], -0.33 to -0.05; $P = 0.0074$), ‘sexually aroused’ (-0.17; 95% CI, -0.30 to -0.03; $P = 0.0154$), and ‘overall sexual satisfaction’ (-0.16; 95% CI, -0.30 to -0.03; $P = 0.0184$).

Implications/Conclusions: There were small changes in prolactin levels, low proportions of patients with postbaseline elevated prolactin values, low incidences of prolactin-related TEAEs, and modest improvements in sexual functioning with adjunctive brexpiprazole in MDD.

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Major depressive disorder (MDD) has a high prevalence and health burden and is a leading cause of disability worldwide.^{1,2}

Many patients do not achieve adequate response or remission with antidepressant therapy (ADT) alone; for such patients, there is evidence supporting the benefits of atypical antipsychotics as adjunctive treatment. As with all treatments, clinicians are recommended to weigh potential benefits with potential risks associated with limited availability of long-term study data.³

Hyperprolactinemia is an undesirable effect of most antipsychotics, although compounds differ greatly in their potential for prolactin elevation. Hyperprolactinemia is considered to be due primarily to dopamine D₂ receptor blockade.^{4,5} Women are more sensitive than men to hyperprolactinemic effects due to estrogen involvement in modulation of prolactin secretion.⁶ Any increase in prolactin levels can lead to patient distress and impaired quality of life (eg, sexual dysfunction, infertility), be stigmatizing (eg, gynecomastia in men, hirsutism and galactorrhea in women), put overall health at risk (eg, osteoporosis), and, ultimately, affect functioning, treatment adherence, and satisfaction.^{7–11}

In addition, impairment in sexual functioning is by itself common in patients with MDD, and ADTs can elicit and exacerbate sexual dysfunction, which may cause impaired quality of life or discontinuation of treatment.¹²

Brexpiprazole is a serotonin–dopamine activity modulator that is a partial agonist at 5-HT_{1A} and dopamine D₂ receptors, and an antagonist at 5-HT_{2A} and noradrenaline α_{1B/2C} receptors, all with subnanomolar affinity.¹³ Brexpiprazole is approved in various countries and regions for the treatment of schizophrenia and as adjunctive therapy to antidepressants for the treatment of MDD.

The current analysis includes pooled data from three short-term, placebo-controlled studies^{14–16} and one long-term, 52-week, open-label extension (OLE) study¹⁷ in patients with MDD, to evaluate the effect of brexpiprazole on prolactin, sexual functioning, and other downstream health/medical effects.

MATERIALS AND METHODS

Study Designs

The studies (Supplementary Table 1 – Supplementary digital content 1, <http://links.lww.com/JCP/A699>) were designed and conducted in accordance with the principles of the Declaration of Helsinki, and study protocols were approved by relevant institutional review boards or independent ethics committees. All patients provided written informed consent before study start, and possible adverse effects were fully explained. The studies were registered at ClinicalTrials.gov.

The short-term studies were randomized, double-blind, placebo-controlled, fixed-dose studies (Pyxis [NCT01360645],¹⁴ Polaris [NCT01360632],¹⁵ and Sirius [NCT02196506]¹⁶), which included an 8-week, single-blind, prospective ADT phase followed by a 6-week, randomized, double-blind, placebo-controlled adjunctive phase. In the prospective treatment phase, eligible patients received an investigator-determined, open-label ADT, together with single- or double-blind placebo. During this phase, patients were assessed for inadequate response to prospective ADT. Patients with inadequate response were randomized to double-blind treatment with adjunctive brexpiprazole (1, 2, or 3 mg) or placebo for 6 weeks. Antidepressant therapy responders continued to receive the same open-label ADT and placebo until the end of the study; these patients were not randomized or included in the short-term analyses.

The long-term study (Orion [NCT01360866])¹⁷ was a flexible-dose (brexpiprazole 0.5–3 mg/d) OLE that enrolled patients completing either Pyxis, Polaris, or Delphinus.¹⁸ Delphinus was a flexible-dose study with an 8- or 10-week, double-blind, prospective phase followed by a 6-week, randomized, double-blind, placebo-controlled, active-referenced (quetiapine XR 150–300 mg/d) phase with flexible dosing of brexpiprazole (2–3 mg/d). Data from Delphinus were not included in the short-term analyses because prolactin was not measured at the same time points as in Pyxis and Polaris, and sexual functioning was not assessed.

Patients in the OLE remained on the same assigned open-label ADT from their parent study. All patients were titrated to brexpiprazole (regardless of previous brexpiprazole exposure): first week, 0.5 mg/d; second week, 1 mg/d; third and fourth weeks, 0.5–2 mg/d; and fifth week onward, 0.5–3 mg/d. From the third week, doses could be adjusted for reasons of efficacy/tolerability according to investigator's judgment. Study duration was changed from 52 to 26 weeks midway through the study because the safety profile was considered well established.

Assessments

In short-term studies, baseline was defined as the last value obtained before randomization. In the OLE, baseline was defined as the last scheduled visit of the short-term study. We studied changes from baseline, clinically relevant prolactin values, and shifts in prolactin status in patients with low, normal, or elevated prolactin levels at baseline.

Prolactin was measured at baseline and at weeks 2, 4, and 6 in Pyxis and Polaris; at baseline and at week 6 in Sirius; and with regular intervals throughout the OLE. Mean and median changes from baseline are reported at week 6 for the short-term studies and at weeks 26 and 52 for the OLE.

Prolactin was measured using a Beckman Coulter Access Prolactin assay (Beckman Coulter Inc, Brea, California).^{19,20} Prolactin normal ranges for females and males were defined as 2.74 to 26.72 ng/mL and 2.64 to 13.13 ng/mL, respectively.¹⁹ Upper limit of normal (ULN) prolactin levels were 26.72 ng/mL for females and 13.13 ng/mL for males.^{19,20} Values below normal range were defined as 'low.' The lower limit of quantitation was 0.25 ng/mL. The inter-assay coefficient of variation was 2.9% to 4.6%, and the inter-assay coefficient of variation was 3.6% to 5.6%. Further details of the prolactin analysis method are given in the supplementary appendix (Details of prolactin analysis – Supplementary digital content 1, <http://links.lww.com/JCP/A699>).

Clinically relevant prolactin values were defined in accordance with regulatory submission documents, that is, any value greater than $1 \times$ ULN. Incidences of shifts in prolactin status are presented as shifts from baseline to anytime postbaseline. Percentages were obtained by dividing the number of patients with potential clinically relevant shift with the total number of patients who met the baseline criteria and had a postbaseline result.

Treatment-emergent adverse events (TEAEs) potentially related to prolactin were searched using the MedDRA 19.0 System Organ Class *Reproductive system and breast disorder* and the preferred terms *blood prolactin increased, hyperprolactinemia, galactorrhea, gynecomastia, breast swelling, breast enlargement, breast mass, breast tenderness, amenorrhea, oligomenorrhea, anovulatory cycle, and hypomenorrhea*.

Sexual functioning was assessed using the patient-rated Massachusetts General Hospital Sexual Functioning Questionnaire (MSFQ), where interest in sex, arousal, ability to achieve orgasm, ability to maintain erection (men only), and overall sexual satisfaction were each scored as 1 (greater than normal), 2 (normal), 3 (minimally diminished), 4 (moderately diminished), 5 (markedly diminished), or 6 (totally absent).²¹

Statistical Analysis

All analyses were performed on the safety population (patients receiving ≥ 1 dose of study medication). Patients in the short-term studies treated with placebo were pooled for the analysis, as were patients treated with fixed-dose brexpiprazole.

Calculation of mean and median prolactin changes in the studies was based on observed case data. Both mean and median values were provided because of skewed distribution of the prolactin values. Values below the lower limit of quantitation were considered missing in calculations of means and medians and were entered as zero into calculations of potentially clinically relevant values and shifts in prolactin status.

A path analysis was performed on observed case data at week 6 of the short-term double-blind treatment period to address the potential issue of pseudospecificity and assess the extent to which improvement in sexual functioning, measured by MSFQ, was a direct treatment effect versus an indirect effect mediated through a general improvement of depressive symptoms, measured as change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score.

The path analysis estimating the treatment effects fitted two analysis of covariance (ANCOVA) models. In the first ANCOVA model, the direct placebo-subtracted effect of brexpiprazole on sexual function was determined based on estimates from a model adjusting for the correlation between changes in MADRS total score and the MSFQ item 'overall sexual satisfaction' score. The placebo-subtracted indirect effect, passing through change in depressive symptoms, was calculated by multiplying the correlation estimate from the first ANCOVA model with the estimates from the second ANCOVA model that estimated the placebo-subtracted effect of treatment on depressive symptoms using the MADRS total score. The placebo-subtracted direct and indirect effects are presented as percentages of total placebo-subtracted effect (direct effect + indirect effect).

RESULTS

Patients

Baseline demographic and clinical characteristics were similar between treatment groups in the short-term studies and by prior treatment in the OLE, except for patients in the prior ADT group (adequate responders) whose MADRS total score at baseline (end of short-term study) was markedly lower (Supplementary Table 2 – Supplementary digital content 1, <http://links.lww.com/JCP/A699>).

Short-Term Studies—Changes From Baseline

Mean (standard deviation [SD]) [median] baseline prolactin values in brexpiprazole-treated patients were 10.06 (5.36) [8.80]

ng/mL for females, and 7.92 (3.78) [7.06] ng/mL for males, and in placebo-treated patients were 10.20 (6.04) [8.37] ng/mL for females, and 7.83 (3.65) [7.22] ng/mL for males.

Mean (SD) [median] changes from baseline to week 6 in brexpiprazole-treated patients were 7.46 (8.92) [5.99] ng/mL for females, and 1.90 (4.42) [1.61] ng/mL for males, and in placebo-treated patients were -0.03 (5.31) [-0.15] ng/mL for females, and 0.24 (3.35) [0.08] ng/mL for males.

Among females with prolactin values within low or normal range at baseline, a small increase was observed in the brexpiprazole groups (Table 1). In females with greater than 1 × ULN prolactin values at baseline, there was a decrease from baseline in both the brexpiprazole and placebo groups. In males, increases over time were small (approximately 2 ng/mL) in patients with low or normal values at baseline. In males with greater than 1 × ULN prolactin values at baseline, a small decrease was observed in the brexpiprazole group, whereas a small increase was seen in the placebo group. There seemed to be a dose-dependent increase in prolactin levels at week 6 for females with normal prolactin levels at baseline, whereas this observation was not as pronounced in male patients (Supplementary Table 3 – Supplementary digital content 1, <http://links.lww.com/JCP/A699>).

Long-Term Study—Changes From Baseline

Mean (SD) [median] baseline prolactin values were 12.20 (10.01) [9.69] ng/mL for females and 8.99 (6.71) [7.50] ng/mL for males.

Mean (SD) [median] changes from baseline to week 52 were 0.47 (8.37) [0.27] ng/mL for females and 0.37 (6.41) [0.27] ng/mL for males.

Among females and males with low or normal values at baseline, a small increase over time was observed (Table 2). There was a small decrease among females in the prior brexpiprazole group at week 52. Prolactin in females and males with greater than 1 × ULN values at baseline tended to decrease over time regardless of the previous treatment given.

Postbaseline Elevated Values and Shifts

The proportion of brexpiprazole-treated patients with postbaseline greater than 3 × ULN prolactin values at any visit in the short-term studies was 0.0% for females and 0.2% for males, and in the placebo-treated patients was 0.3% for females and 0.2% for males. The proportion of patients with postbaseline greater than 3 × ULN prolactin values at any visit in the OLE was 0.5% for females and 0.8% for males.

Larger proportions of patients on brexpiprazole than placebo shifted from low or normal to greater than 1 × ULN in the short-term studies (Supplementary Table 4 – Supplementary digital content 1, <http://links.lww.com/JCP/A699>); this proportion was slightly larger in males than in females during long-term treatment. A shift from normal at baseline to greater than 3 × ULN was observed in less than 1% of patients, regardless of study length. Four percent of males with low levels at baseline shifted to greater than 3 × ULN in the OLE.

There were 36.4% of females and 18.8% of males in the brexpiprazole group with greater than 1 × ULN prolactin values at baseline who had normalized prolactin values during the short-term studies; corresponding proportions in the OLE were 32.4% and 21.7%. The majority (range, 77.6% to 82.0%) of brexpiprazole-treated patients with normal prolactin values at baseline did not shift during the studies.

TABLE 1. Short-Term Studies—Mean Changes From Baseline in Prolactin (ng/mL) by Sex and Baseline Prolactin Status

Sex	Females						Males						
	Baseline Status		Low		>1 × ULN		Normal		Low		>1 × ULN		
	Treatment	n	Placebo	Brexpiprazole 1–3 mg	Placebo	Brexpiprazole 1–3 mg	Placebo	Brexpiprazole 1–3 mg	Placebo	Brexpiprazole 1–3 mg	Placebo	Brexpiprazole 1–3 mg	
Baseline													
Mean			2.29	2.17	9.68	9.66	31.92	33.72	2.42	2.44	7.26	7.23	17.46
(SD)			(0.31)	(0.79)	(4.70)	(4.38)	(4.65)	(6.18)	(0.04)	(0.07)	(2.41)	(2.29)	(5.32)
[Median]			[2.30]	[2.17]	[8.29]	[8.70]	[31.57]	[32.05]	[2.42]	[2.44]	[7.09]	[6.92]	[16.63]
n			4	2	398	555	11	10	2	2	166	222	11
Change week 6													
Mean			1.31	4.87	0.27	7.75	-7.34	-13.08	0.86	2.36	0.22	2.29	0.39
(SD)			(1.00)	(0.86)	(4.75)	(8.60)	(13.51)	(10.74)	(0.99)	(2.06)	(2.62)	(3.68)	(9.05)
[Median]			[1.35]	[4.87]	[-0.15]	[6.19]	[-12.88]	[-14.03]	[0.86]	[2.36]	[0.04]	[1.71]	[1.90]
n			4	2	381	522	10	9	2	2	156	207	11

TABLE 2. Long-Term Study—Mean Changes From Baseline in Prolactin (ng/mL) by Sex, Baseline Prolactin Status, and Prior Treatment

Treatment	Baseline Status			Low			Normal			>1× ULN		
	Prior placebo	Prior brexpiprazole	Prior quetiapine	Prior placebo	Prior brexpiprazole	Prior ADT	Prior quetiapine	Prior ADT	Prior brexpiprazole	Prior quetiapine	Prior ADT	Prior quetiapine
Females												
Baseline	2.33	—	—	9.40	13.81	9.87	9.03	40.32	39.63	42.43	39.16	39.16
Mean	(0.19)	(0.75)	(0.75)	(4.62)	(5.97)	(4.82)	(4.16)	(28.76)	(21.00)	(22.94)	(19.94)	(19.94)
(SD)	[2.28]	[2.45]	[2.45]	[8.56]	[13.62]	[8.59]	[8.49]	[29.96]	[34.20]	[32.43]	[30.23]	[30.23]
[Median]	3	14	14	345	421	1040	45	15	53	34	4	4
n	Change week 26;											
Mean	5.23	—	—	5.94	0.64	3.63	3.27	-8.72	-14.81	-18.29	-25.22	-25.22
(SD)	(0)	(2.68)	(2.68)	(9.92)	(15.11)	(7.86)	(6.45)	(33.02)	(28.39)	(28.30)	(23.93)	(23.93)
[Median]	[5.23]	[3.54]	[3.54]	[4.99]	[-0.98]	[2.30]	[2.54]	[-4.73]	[-12.73]	[-13.62]	[-16.80]	[-16.80]
n	1	10	10	225	284	754	34	10	33	26	4	4
Change week 52;												
Mean	—	—	—	4.08	-2.20	3.01	1.66	-13.56	-12.57	-8.18	—	—
(SD)	(0)	(0)	(0)	(7.22)	(7.00)	(6.05)	(0)	(2.50)	(12.41)	(21.21)	(21.21)	(21.21)
[Median]	[2.29]	[2.29]	[2.29]	[2.70]	[-2.41]	[2.20]	[1.66]	[-14.28]	[-12.20]	[-9.84]	[-9.84]	[-9.84]
n	1	1	1	113	180	184	1	4	22	6	6	6
Males												
Baseline	1.62	1.96	—	6.88	8.04	7.07	6.64	20.54	17.67	23.05	30.31	30.31
Mean	(0.96)	(0.75)	(0.92)	(2.63)	(2.38)	(2.46)	(2.01)	(8.91)	(4.91)	(13.61)	(21.39)	(21.39)
(SD)	[2.01]	[1.96]	[2.26]	[6.54]	[8.19]	[6.69]	[6.14]	[18.21]	[15.85]	[16.99]	[30.31]	[30.31]
[Median]	5	2	10	125	185	457	23	17	37	66	2	2
n	Change week 26;											
Mean	5.57	5.50	2.53	2.24	0.66	2.11	6.87	-7.14	-1.80	-4.44	—	—
(SD)	(7.01)	(0)	(1.55)	(3.39)	(5.05)	(5.08)	(10.06)	(13.16)	(9.10)	(13.98)	(13.98)	(13.98)
[Median]	[3.34]	[5.50]	[2.69]	[1.89]	[-0.21]	[1.37]	[2.32]	[-4.80]	[-2.75]	[-3.05]	[-3.05]	[-3.05]
n	4	1	7	86	118	337	13	13	24	53	53	53
Change week 52;												
Mean	1.48	—	2.81	2.97	0.35	1.07	—	-5.78	-5.01	-1.63	—	—
(SD)	(0.73)	(0.73)	(2.88)	(5.62)	(4.03)	(3.32)	(4.08)	(4.08)	(5.36)	(17.27)	(17.27)	(17.27)
[Median]	[1.48]	[1.48]	[2.81]	[1.41]	[-0.40]	[0.89]	[-4.07]	[-6.43]	[-4.07]	[-3.09]	[-3.09]	[-3.09]
n	2	2	2	46	71	74	8	8	20	16	16	16

Treatment-Emergent Adverse Events Related to Hyperprolactinemia

The incidence of TEAEs related to hyperprolactinemia was low (Supplementary Table 5 – Supplementary digital content 1, <http://links.lww.com/JCP/A699>). Four (0.7%) of the 613 patients in the placebo group and 26 (3.1%) of the 835 patients in the brexpiprazole 1 to 3 mg group in the short-term studies experienced TEAEs related to hyperprolactinemia or sexual functioning.

The incidence of prolactin-related and sexual functioning TEAEs in the OLE was 3.1% (92/2938). The most common TEAE related to hyperprolactinemia in the short-term studies and OLE was blood prolactin increased, with an incidence of 1.6% and 0.7%, respectively. Patients who developed a prolactin increase greater than $3 \times$ ULN during the short-term studies did not report TEAEs related to hyperprolactinemia or sexual functioning, whereas in the OLE, two patients experienced one TEAE each (blood prolactin increased).

Sexual Functioning

In the short-term studies, all MSFQ items showed numerical decreases from baseline to week 6 (Figs. 1A, B), indicating overall improvement in sexual functioning for females and males after treatment with brexpiprazole. There were statistically significant improvements for brexpiprazole versus placebo in females on the items ‘interest in sex’ (-0.19 ; 95% confidence interval [CI], -0.33 to -0.05 ; $P = 0.0074$), ‘sexually aroused’ (-0.17 ; 95% CI, -0.30 to -0.03 ; $P = 0.0154$), and ‘overall sexual satisfaction’ (-0.16 ; 95% CI, -0.30 to -0.03 ; $P = 0.0184$) (Fig. 1A); this result was driven by females with normal prolactin levels at baseline (the largest subgroup) (Supplementary Figure 1A – Supplementary digital content 1, <http://links.lww.com/JCP/A699>). In males, there were no statistically significant differences between brexpiprazole and placebo, in the full sample (Fig. 1B) or when split by baseline prolactin level (Supplementary Figure 1B – Supplementary digital content 1, <http://links.lww.com/JCP/A699>).

In the OLE, all MSFQ items showed numerical improvements from baseline to week 52 (Fig. 1C), except in males with low prolactin levels at baseline for ‘sexually aroused’ and ‘maintain erection’ (Supplementary Figure 1C – Supplementary digital content 1, <http://links.lww.com/JCP/A699>). Improvements were numerically larger in females than in males in the total population (Fig. 1C), and in patients with low and normal prolactin levels at baseline (Supplementary Figure 1C – Supplementary digital content 1, <http://links.lww.com/JCP/A699>); the opposite situation was observed in patients with high prolactin levels, where males displayed numerically larger improvements compared with females.

The path analysis (Path analysis results – Supplementary digital content 1, <http://links.lww.com/JCP/A699>) revealed that at week 6 in the short-term studies, 55.3% of the total placebo-subtracted effect of brexpiprazole on ‘overall sexual satisfaction’ was a direct placebo-subtracted effect, whereas 44.7% of the total placebo-subtracted effect was an indirect placebo-subtracted effect, mediated via improvements in depressive symptoms as assessed with the MADRS.

DISCUSSION

This analysis of short- and long-term data from patients with MDD and inadequate response to antidepressants showed small mean increases from baseline in prolactin levels and low proportions of patients with elevated prolactin levels after treatment with brexpiprazole adjunctive to ADTs. Most of the patients did not shift from normal prolactin levels at baseline. The incidence of TEAEs related to hyperprolactinemia and sexual dysfunction

was low. Overall, the changes in prolactin levels observed were not considered to be of clinical importance.

In the short-term studies, sexual functioning improved in both females and males, with statistically significant improvements for brexpiprazole versus placebo in females in 3 of 4 items of the MSFQ. In the OLE, all items of the MSFQ showed improvements from baseline. Improvements in sexual functioning for women and men were numerically larger during long-term than short-term treatment. The positive effect of brexpiprazole on sexual functioning, as investigated using the MSFQ item ‘overall sexual satisfaction’ in the short-term studies, seemed to be mainly a direct effect and, to a lesser extent, mediated via improvements in depressive symptoms.

The present results agree with a previous prolactin analysis in schizophrenia,²² thereby confirming that brexpiprazole has a small impact on prolactin levels in patients with MDD, as well as in patients with schizophrenia. In the absence of a network meta-analysis in MDD that includes brexpiprazole, a network meta-analysis of oral antipsychotics in schizophrenia can be used to make an indirect comparison of the effects of different agents on prolactin.²³ This analysis showed that brexpiprazole did not differ significantly from placebo in terms of prolactin elevation (mean difference, 0.95 ng/mL), whereas, for example, risperidone and paliperidone were associated with significantly elevated prolactin levels (mean difference, 37.98 and 48.51 ng/mL, respectively).²³

An indirect comparison with aripiprazole regarding effects on prolactin and sexual functioning in MDD is warranted, given the similarities in the D₂ receptor binding profile. Like brexpiprazole, aripiprazole is a D₂ partial agonist, and aripiprazole is often referred to as a prolactin-sparing compound, producing little or no clinically significant prolactin elevation.²⁴ In aripiprazole schizophrenia trials, decreases from baseline in mean prolactin levels have been observed in short- and long-term studies.^{25–27} Aripiprazole adjunctive to ADTs in patients with MDD seems to have a similar minimal effect on prolactin as in schizophrenia, whereas, for example, risperidone fared worse than placebo.²⁸ Indirect comparisons with published data on aripiprazole^{29–31} suggest no relevant differences between brexpiprazole and aripiprazole.

Investigation of the effects of adjunctive aripiprazole on sexual functioning in patients with MDD and inadequate response to antidepressants demonstrated modest beneficial effects on sexual functioning in women, largely unrelated to changes in depressive symptoms and without consistent correlation to prolactin levels.³² Perhaps not surprisingly, the results from our analysis of brexpiprazole and sexual functioning are quite similar.

Dopamine, norepinephrine, and melanocortins stimulate attention and desire in women.³³ Compared with aripiprazole, brexpiprazole is more potent at 5-HT_{1A/2A} receptors, has higher affinity for the noradrenaline $\alpha_{1B/2C}$ receptors, and shows lower intrinsic activity at the D₂ receptor.¹³ However, as all atypical antipsychotics are dopamine blocking agents, and despite brexpiprazole having intrinsic activity at the D₂ receptor, it is perhaps more reasonable to speak of an expected lack of harmful effects on sexual functioning with brexpiprazole, rather than improvements. Nevertheless, significant improvements in sexual functioning in women treated with adjunctive brexpiprazole were in fact seen not only for the items ‘interest in sex’ and ‘overall sexual satisfaction’ as with aripiprazole, but also for ‘sexually aroused.’

Although indirect comparisons between drugs should be performed with caution, this difference could possibly be explained by brexpiprazole being more potent at 5-HT_{1A/2A} receptors than aripiprazole. The 5-HT_{2A} antagonist effects of brexpiprazole, similar to those of flibanserin (approved for the treatment of hypoactive sexual desire disorder in women³⁴), and possibly also

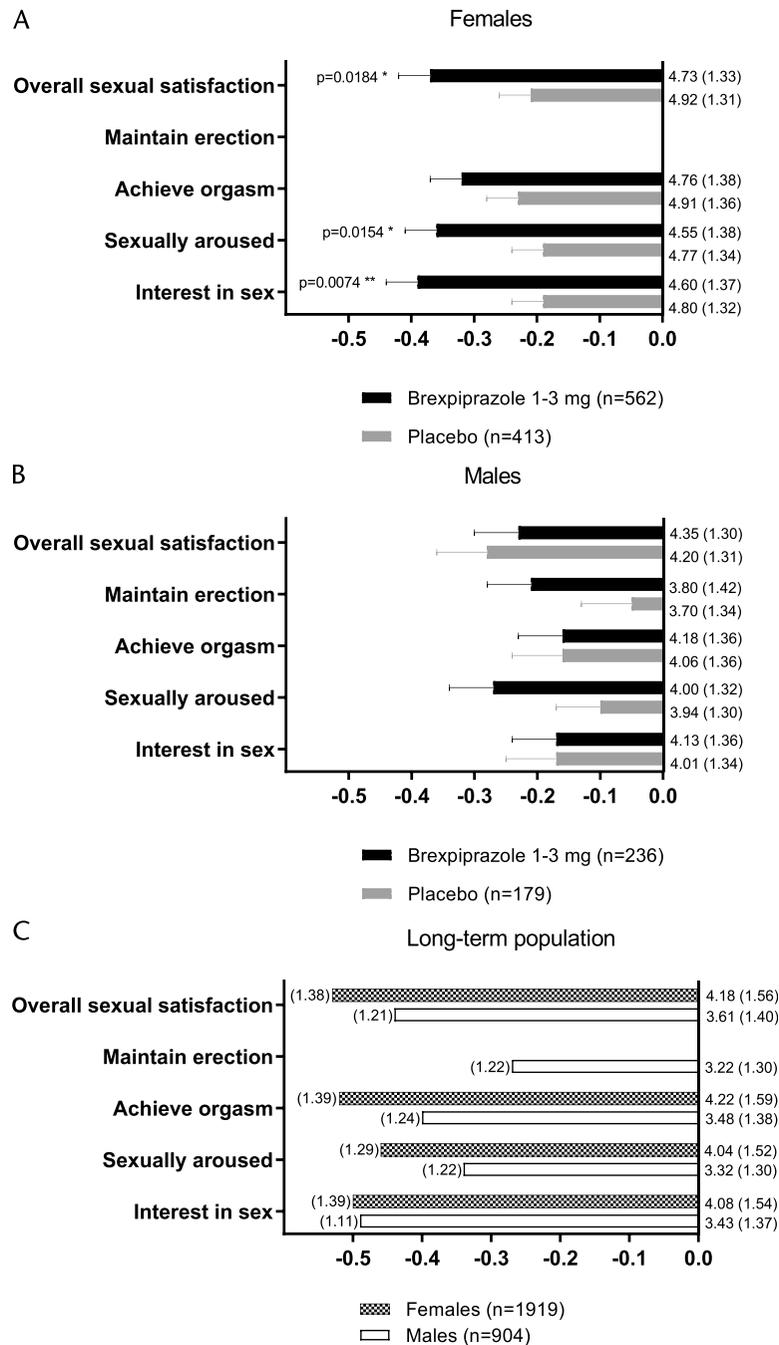


FIGURE 1. Summary of least squares mean (standard error) change (short-term studies) or mean (SD) change (long-term study) from baseline in MSFQ item scores by sex. Lower/decreased MSFQ scores indicate better/improved sexual functioning. Numbers below graphs represent number of patients at baseline. Mean (SD) baseline item scores are given at the vertical axis by each bar.

the 5-HT_{1A} partial agonist effects, might potentially attenuate the effects of serotonin reuptake inhibition from selective serotonin reuptake inhibitor antidepressants on desire and arousal by decreasing serotonin activity,³⁵ and thereby contribute to the positive effect on the item ‘sexually aroused.’

As for the differences in magnitude of improvements in sexual functioning between women and men in our analysis, serotonin inhibition of sexual functioning may exert a greater impact in women due to the mitigating effects of testosterone in men. Similarly, women are more sensitive than men to hyperprolactinemic effects

of antipsychotic drugs due to estrogen involvement in modulation of prolactin secretion.⁶ Of note is that, in female patients with elevated prolactin at baseline, almost a third had normalization of prolactin values with continued brexipiprazole treatment in the OLE.

Limitations of our analysis should be taken into consideration and include the use of a post hoc analysis approach, evaluation of patients fulfilling eligibility criteria limits generalizability, lack of head-to-head comparisons with other adjunctive antipsychotics, the potentially limited ability to assess changes in sexual functioning within the relatively short time frame of the short-term studies,

and, finally, the MSFQ not having been validated in women, so differences might be related, at least in part, to the scale rather than measurable medication effects. A strength of the analysis is that it is based on a large, high-quality data set.

In conclusion, patients in this analysis had small changes in prolactin levels and few adverse events related to hyperprolactinemia and sexual dysfunction after adjunctive treatment with brexpiprazole. Brexpiprazole had a modest, although significant, positive effect on several components of sexual functioning in women—interest in sex, arousal, and overall sexual satisfaction. General improvements in overall sexual satisfaction were not primarily driven by improvements in depressive symptoms.

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